UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte RICHARD P. BLYE and HYUN K. KIM

Appeal 2007-1821
Application 11/040,964
Technology Center 1600

Decided: June 1, 2007

Before ERIC GRIMES, LORA M. GREEN, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

LEBOVITZ, *Administrative Patent Judge*.

DECISION ON APPEAL

This is a decision on appeal from the final rejection of claims 75-80 and 82-86. We have jurisdiction under 35 U.S.C. § 6(b). We affirm.

STATEMENT OF CASE

The claims are drawn to a single compound, 7α,11β-dimethyl-17β-hydroxyestr-4-en-3-one 17-undecanoate. This compound is a synthetic androgen which is used as a substitute for testosterone (Specification 1: ¶¶ 4, 13). Its structure is shown in Fig. 12 of the instant disclosure.

Claims 75-114 are pending (Br. 2). Claims 81 and 87-114 are withdrawn from consideration as being drawn to an unelected invention (Br. 2). Claims 75-80 and 82-86 stand finally rejected over prior art (Br. 2). The Examiner relies on the following prior art as evidence of unpatentability:

Herr '863	US 2,806,863	Sep. 17, 1957
Herr '517	US 2,837,517	Jun. 3, 1958
Lasdon	GB App. 957,953	May 13, 1964
Herr '644	US 3,160,644	Dec. 8, 1964
Machlin	US 3,438,783	Apr. 15, 1969
Cook	US 5,952,319	Sep. 14, 1999

Claims 75-80 and 82-86 stand rejected under 35 U.S.C. § 103(a) as obvious over Cook (Answer 3). Appellants argue claims 75-80, 85, and 86 separately from claims 82-84 (Br. 3). Within each grouping, Appellants do not provide separate reasons for the patentability of any individual claim. Consequently, the claims in each grouping stand or fall together. We select claims 75 and 82 as representative. 37 C.F.R. § 41.37(c)(1)(vii). Claims 75 and 82 read as follows:

> 75. An oral dosage formulation comprising 7α,11β-dimethyl-17β-hydroxyestr-4-en-3-one 17-undecanoate and a pharmaceutically-acceptable carrier.
>
> 82. 7α,11β-dimethyl-17β-hydroxyestr-4-en-3-one 17-undecanoate (Compound II) in crystalline form.

THE PRIOR ART

The Examiner summarizes Cook as follows:

> Cook teaches a generic group of androgenic steroids having enhanced activity relative to testosterone (see the entire disclosure, especially formula (I), col. 2, line 66 - col. 4, line 4; col. 9, line 65 - col. 10, line 40; col. 17, Example 3; col. 19, line

> 48 - col. 21, line 6; claims 1 and 2). The reference exemplifies R^4 groups such as n-C_6H_{13} and n-C_9H_{19} (see especially col. 22, claim 2). The reference teaches (a) administration of from about 5% to about 120% of a conventional dosage of a conventional drug and (b) various formulation[s] such as for oral, dermal or nasal administration (see col. 19 line 49 - col. 20, line 65).

(Answer 3-4.)

In making an obviousness determination, it is necessary to identify the differences between the claimed invention and the prior art. In this case, Cook teaches 7α,11β-dimethyl nortestosterone enanthate (Cook, col. 17, ll. 34-36) which has an n-C_6H_{13} alkyl group at its 17-position. The claimed invention has the same structure, but differs in having an n-$C_{10}H_{21}$ alkyl group at its 17-position (Specification, Fig. 12 showing $(CH_2)_9CH_3$). The Examiner contends

> . . . because (a) of the close structural similarity of the exemplified reference compound (see col. 22, claim 2) and the claimed compound and (b) the teaching by the reference that R^4 can be a C_{1-18} alkyl (see col. 21, claim 1), the claimed compound would have been obvious to the skilled artisan in the art at the time of the present invention. The motivation to make the claimed compound would be based on the desire to make additional androgenic compounds having enhanced activity as taught by Cook.

(Answer 4.)

DISCUSSION

Appellants do not dispute in this appeal the Examiner's finding that the claimed compound would have been prima facie obvious from Cook's teachings. Instead, they challenge the rejection on the grounds: 1) that the claimed oral formulation would not have been obvious; 2) that Appellants' invention satisfies a long-felt need; 3) that the claimed invention possesses

advantages over the prior art; and 4) that evidence of unexpected results establishes patentability of the claimed invention. We address each of these arguments, in turn, below.

The compounds described by Cook and Appellants are referred to by a variety of names in the various documents in this proceeding. For clarity, we adopt Cook's nomenclature. The claimed compound – 7α,11β-dimethyl-17β-hydroxyestr-4-en-3-one 17-undecanoate – in Cook's nomenclature is 7α,11β-dimethyl nortestosterone undecanoate. This compound has an n-$C_{10}H_{21}$ alkyl group at its 17-position. Synonyms are: CDB-4521, dimethandrolone undecanoate, and the 17-undecanoate ester.

The compound in Cook is 7α,11β-dimethyl nortestosterone enanthate. This compound has an n-C_6H_{13} alkyl group at its 17-position. Synonyms are: the enanthate ester of 7α,11β-dimethyl nortestosterone, CDB-1422, dimethandrolone heptanoate, and the 17-enanthate ester.

1. Claims 75-80, 85, and 86

No reasonable expectation of success that the claimed compound would be orally active

Claim 75 is directed to an "oral dosage formulation." Appellants argue that there was no reasonable expectation of success that the claimed compound would have activity when orally administered, and thus an oral composition would not have been obvious to a person of ordinary skill in the art (Br. 4).

We do not find this argument persuasive. First, Cook teaches that its compounds can be administered orally (Cook, col. 19, 11. 49-50). We see

no evidence in the record that this statement would not apply equally to all Cook's compounds, including the 7α,11β-dimethyl nortestosterone enanthate of Example 3. Secondly, Appellants acknowledge that orally active androgens were known in the art, including androgens with long-chain esters. In the declaration dated December 1, 2005 (Blye 1 Declaration (Exhibit 1)), the declarant Dr. Blye states:

> The first of these, CDB-4386 the bucyclic acid ester, was submitted for testing on April 6, 1998. I, as the Project Officer for the Biological Testing Facility contract, ordered assay for androgenic activity by both the oral and parenteral (subcutaneous) routes. The compound was found to be several times more active than methyltestosterone standard when administered orally. This observation was cause for some rejoicing since the then prevailing knowledge was that long-chain esters of androgenic steroids did not exhibit potent oral activity.

(Blye 1 Declaration 4: ¶ 11.) Thus, the skilled worker – as the Examiner contends (Answer 6) – would have had reason to test other synthetic androgens for oral activity and an expectation that such androgens would be orally-active. Success does not have to be guaranteed as long as the skilled worker would have perceived a reasonable likelihood of success. *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1295, 80 USPQ2d 1001, 1007 (Fed. Cir. 2006).

Finally, we note that Appellants admit that there was a need for oral androgens (Br. 5; Reply Br. 7).

> When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of

> innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. __, 82 USPQ2d 1385, 1397 (2007). It is our opinion that oral administration was a known option that would have been obvious to try.

Appellants' invention meets a long-felt need

Appellants also argue that "the presently claimed invention provides a solution to a long-felt need, i.e., an orally active and parenterally long-acting androgen" (Br. 5).

In making an obviousness determination, the Supreme Court instructs us "to look at any secondary considerations that would prove instructive." *KSR*, 82 USPQ2d at 1395. Among these considerations is "long felt but unsolved needs." *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). "[P]recedent requires that the applicant submit actual evidence of long-felt need." *In re Kahn*, 441 F.3d 977, 990, 78 USPQ2d 1329, 1338-39 (Fed. Cir. 2006). In this case, Appellants assert that "the presently claimed invention provides a solution to a long-felt need, i.e., an orally active and parenterally long-acting androgen" (Br. 5). As evidence of this, a declaration under 37 C.F.R. § 1.132 is provided by co-inventor Dr. Richard Blye (Blye 1 Declaration) which Appellants assert shows that "others have failed to produce an orally active and parenterally long-acting androgen" (Br. 5).

The relevant secondary consideration is "long-felt but unsolved need." The first question is whether there is evidence of a "long-felt need."

Secondly, the question is whether there is evidence that Appellants have solved the need.

We do not find adequate evidence in the Blye 1 Declaration that there was a long-felt need for a parenterally long-acting androgen as asserted in Appellants' Brief. In paragraph 4 of his declaration, Dr. Blye refers to a "long-felt need for an oral androgen," but does not mention a long-felt need for a *long-acting androgen* (Blye 1 Declaration 2: ¶ 4). Later in the declaration, Dr. Blye states that the Population Council asked his group ("we") to "make an ester which might prove long-acting upon parenteral administration" (Blye 1 Declaration 3: ¶ 7). However, Dr. Blye does not assert or explain how the Population Council's request is evidence of a long-felt need.

Dr. Blye states that 7α,11β-dimethyl-19-nortestosterone enanthate (CDB-1422) was synthesized by the Research Triangle Institute (RTI) (Blye 1 Declaration 3: ¶¶ 8-9). This compound differs from the claimed compound in having the n-C_6H_{13} group at the 17-position rather than n-$C_{10}H_{21}$ as in the claimed compound. It is the same compound described in Example 3 of Cook (Cook, col. 17, l. 34 to col. 18, l. 3). Dr. Blye states that a duration test[1] was performed for this compound, but does not describe the results of this test (Blye 1 Declaration 3: ¶ 9)

Evidence of the activity of 7α,11β-dimethyl-19-nortestosterone enanthate (CDB-1422) is, in fact, shown in Cook (Cook, cols. 19-20) and in Dr. Blye's second declaration (Blye 2 Declaration (Exhibit 3)). Cook's Table 2 (Cook, cols. 19-20) establishes that 7α,11β-dimethyl-19-

[1] We presume that the "duration test" is a test for "long-acting" activity.

nortestosterone enanthate has activity over a ten-week period. Exhibit A of the Blye 2 Declaration also shows 7α,11β-dimethyl-19-nortestosterone enanthate having activity over this same length of time. Dr. Blye does not define the characteristics of what is considered to be long-acting. But Cook's Table 2 (Cook, cols. 19-20) describes the results as "Long Term Androgenic Activity." Thus, Appellants did not solve the need for a long-acting compound because such a compound – 7α,11β-dimethyl-19-nortestosterone enanthate – already existed in the prior art.

Appellants also contend that a long-felt need for an *oral* androgen was stated to have been appreciated in the prior art. Our difficulty with this argument is that Dr. Blye admits in his declaration that orally active androgens were known in the prior art (Blye 1 Declaration 4: ¶ 11.) Thus, we do not find sufficient evidence to establish a long-felt need for an oral androgen.

The claimed compound has advantages over the prior art

Appellants also argue that the claimed compound has advantages over prior art compounds (Br. 5-7). They assert that prior art compounds have been linked to liver toxicity, but that the claimed compound lacks such toxicity (Br. 6-7).

To rebut prima facie obviousness, the evidence must be of an unexpected difference in properties as compared to the prior art, not merely a showing of an advantage. See *In re Hoch*, 428 F.2d 1341, 1343, 166 USPQ 406, 409 (CCPA 1970). In this case, Appellants assert that an advantage of the claimed compound is that it lacks "an alkyl group at the 17-

alpha position which has been linked to liver toxicity" (Br. 7). We do not find this argument persuasive for several reasons. First, the asserted advantage is a latent property of a compound which is suggested by Cook. "Mere recognition of latent properties in the prior art does not render nonobvious an otherwise known invention." *In re Baxter Travenol Labs.*, 952 F.2d 388, 392, 21 USPQ2d 1281, 1285 (Fed. Cir. 1991). Secondly, the prior art already teaches 7α,11β-dimethyl-19-nortestosterone enanthate, which lacks an alkyl group at the 17-alpha position, and thus would not possess the toxic group that has been asserted to have been linked to liver toxicity.

Summary

In sum, for the reasons articulated by the Examiner, we find that the claimed compound would have been obvious to a person of ordinary skill in the art at the time the application was filed. Appellants have not provided sufficient evidence of secondary considerations to rebut the obviousness of the claimed compound. We affirm the rejection of claim 75. Claims 76-80 fall with claim 75.

2. Claims 82-84

Claims 82-84 are directed to 7α,11β-dimethyl-17β-hydroxyestr-4-en-3-one 17-undecanoate "in crystalline form."

The Examiner asserts:

> (a) Cook teaches the purification of the compounds (see especially Example 3) and (b) purification by crystallization is routine in the chemical and pharmaceutical arts and, thus, it

> would have been obvious to the skilled artisan in the art at the time of the present invention. The skilled artisan would be motivated to obtain a compound having high purity, including a 99% purity, in order to eliminate or reduce adverse effects that might be due to the presence of impurities.

(Answer 4-5.)

> Appellants contend:
>
> Cook et al. fails to identify or suggest to those of ordinary skill in the art a crystallization step as a route to obtaining improved parenteral activity. There is no connection or pointer in the reference between parenteral activity and crystallinity. Obviousness cannot be predicated on what is unknown. Motivation to purify cannot suggest a method for obtaining long-acting parenteral activity.

(Br. 8.)

> We agree with the Examiner.
>
> The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art. Under the correct analysis, any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.

KSR, 82 USPQ2d at 1397. Thus, obviousness does not require that the Examiner find a teaching in the prior art that crystallization was known to improve parenteral activity as demanded by Appellants. Rather, any reason to accomplish crystallization is sufficient to establish obviousness of the claimed subject matter. Here, the Examiner has provided a sound reason for crystallizing the claimed compound: to have a compound of high purity in order to eliminate or reduce adverse effects. Appellants have not identified any flaw in this reasoning, and we find none. Instead, Appellants argue that

the Examiner erred in not finding the same reason in the prior art which motivated Appellants to have made their invention. This is not required to establish obviousness.

Unexpected results

Appellants contend that the claimed compound has "unexpected and superior properties" compared to Cook's 7α,11β-dimethyl nortestosterone enanthate (Br. 9). The Blye 2 Declaration describes an experiment in which the claimed compound ("CDB-4521") and Cook's compound ("CDB-1422") were tested for androgenic activity as a function of time (Blye 2 Declaration 2: ¶ 6). The claimed compound was administered subcutaneously as crystalline needles in an aqueous suspending vehicle (Blye 2 Declaration 2: ¶ 6; Exhibit A). Cook's compound was provided in oil and administered in sesame oil (Blye 2 Declaration 2: ¶ 5; Exhibit A).

Exhibit A is a graph showing the effect of each compound on rat ventral prostate weight. The area under the curve (AUC) is a measure of activity. After the first week, the ventral prostate weight gain and AUC were greater for the claimed compound than for the Cook's compound. Dr. Blye concludes that "[t]he foregoing shows that . . . [the claimed compound] has superior properties compared to the . . . [compound] of Cook" (Blye 2 Declaration 2: ¶ 6).

"[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *In re Baxter Travenol Labs.*, 952 F.2d 388, 392, 21 USPQ2d 1281,

1285 (Fed. Cir. 1991). Therefore, we must first address whether Cook's compound represents the closest prior art.

The Examiner contends that the closest prior art is the lower adjacent homolog of the claimed compound, i.e., the 17-decanoate ester, where the alkyl group is n-C_9H_{19}, as listed in Cook's claim 2 (Cook, col. 22).

Appellants contend that the closest prior art is the 17-enanthate ester of 7α,11β-dimethyl-19-nortestosterone (where the alkyl group is n-C_6H_{13}) because it represents the closest exemplified embodiment described in Cook (Reply Br. 5-6). They argue that the 17-decanoate ester is not specifically exemplified in Cook, but only arrived at after choosing from a menu of choices available in claim 2, including the choice of R^4 to be n-C_9H_{19} from a list of seven different alkyl groups (Reply Br. 6).

In our opinion, Appellants were justified in choosing 7α,11β-dimethyl-19-nortestosterone enanthate as the closest prior art. Appellants are not required to compare the claimed invention with subject matter that does not exist in the prior art. *In re Geiger*, 815 F.2d 686, 690, 2 USPQ2d 1276, 1279 (Fed. Cir. 1987) (Newman, J., concurring). *See* also *Ex parte Westphal*, 223 USPQ 630 (BPAI 1983). In this case, the closest exemplified compound in Cook is the 7α,11β-dimethyl-19-nortestosterone enanthate.

Having determined that Appellants have compared their compound to the closest prior art, we turn to the question of whether Appellants' evidence is sufficient to establish unexpected results. Because the Examiner erred in not considering Appellants' evidence, we designate this as a new ground of rejection under 37 C.F.R. § 41.50(b).

Once prima facie obviousness has been established, an applicant for a patent can rebut it with "a showing of 'unexpected results,' i.e., to show that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected. The basic principle behind this rule is straightforward – that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious." *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995). In this case, we find insufficient evidence that the duration test results described by Dr. Blye were "surprising" to a person of ordinary skill in the art.

The "unexpected results" are based on a comparison of the claimed compound to Cook's 7α,11β-dimethyl-19-nortestosterone enanthate in an experiment designed to determine long lasting activity when administered parenterally to rats (Br. 4). To begin our analysis, we consider what degree of androgenic activity the skilled worker would have expected the 7α,11β-dimethyl-19-nortestosterone enanthate to possess – the compound which Appellants admit to be the closest prior art. Cook states:

> The further importance of the concomitant 11β-methyl group is shown by the androgenic RBA of 194 for 7β,11β-dimethyl-19-nortestosterone and the marked increase in acute androgenic activity of this compound as compared with 7α-methyl-19-nortest[ost]erone (see Table 1) and *of the greater potency and longer duration of action of the enanthate ester of 7α,11β-dimethyl-19-nortestosterone as compared with testosterone enanthate* (See Table 2).

(Cook, col. 18, ll. 43-52.) (Emphasis added.) Table 2 (Cook, col. 19-20) shows that the 7α,11β-dimethyl-19-nortestosterone enanthate (the compound asserted by Appellants to be the closest prior art) was active over a ten-week

period in the same type of assay described in the Blye 2 Declaration, and using the same dosage (0.6 mg). This activity is characterized by Cook as "Long Term Androgenic Activity" (cols. 19-20, Table 2).

It is reasonable to presume that structurally similar chemical compounds have similar properties. *See In re Dillon*, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990); *Soni*, 54 F3d at 749-50, 34 USPQ2d at 1687. From Cook's teaching that 7α,11β-dimethyl-19-nortestosterone enanthate has long term androgenic activity, a person of ordinary skill in the art would have reasonably presumed that structurally similar compounds, including compounds differing only in the length of the 17-position alkyl chain, would also possess long-term activity. Accordingly, in our opinion, the evidence presented in the Blye 2 Declaration that the claimed 7α,11β-dimethyl-19-nortestosterone undecanoate is long-acting would have been expected by a person of ordinary skill in the art from Cook's disclosure of a structurally similar long acting nortestosterone.

Appellants have not provided sufficient evidence that the superiority of the claimed compound over Cook's enanthate would have been *surprising* to a person of ordinary skill in the art – a necessity to establish unexpected results. Appellants have not explained the degree of difference between the claimed compound and Cook's. They show that its activity as determined by AUC is greater than Cook's enanthate, but they do not explain why an increase in activity would be surprising, rather than the normal expected differences in activity between different compounds. Their own Specification shows variations between the claimed 7α,11β-dimethyl-19-

nortestosterone undecanoate and the related bucyclate (e.g., Specification, compare Fig. 5 to Fig. 15).

Finally, Dr. Blye calls the results "superior" (Blye 2 Declaration 1: ¶ 4), but falls short of characterizing them as "unexpected" or "surprising." In their Brief, Appellants state that "[a]s set forth in Exhibit 3, paragraph 4-6, the ... [claimed compound] has unexpected and superior properties" (Br. 9). However, Dr. Blye never uses the term "unexpected" in describing his results. "Mere improvement in properties does not always suffice to show unexpected results." *Soni*, 54 F3d at 751, 34 USPQ2d at 1688.

In sum, we find that Cook's teaching that the 7α,11β-dimethyl-19-nortestosterone enanthate was active over a ten-week period would have led a person of ordinary skill in the art to reasonably expect that claimed compound, which is structurally similar to Cook's compound, would possess long-acting androgenic properties. Appellants have not demonstrated against this baseline expectation that a person of skill in the art would have found the results set forth in Blye 2 Declaration unexpected and surprising to a person of ordinary skill in the art.

For the foregoing reasons, we affirm the rejection of claim 82. Because they were not separately argued, claims 83 and 84 fall with claim 80.

TIME PERIOD

Regarding the affirmed rejection(s), 37 C.F.R. § 41.52(a)(1) provides "[a]ppellant may file a single request for rehearing within two months from the date of the original decision of the Board."

In addition to affirming the examiner's rejection(s) of one or more claims, this decision contains a new ground of rejection pursuant to 37 C.F.R. § 41.50(b) (effective September 13, 2004, 69 Fed. Reg. 49960 (August 12, 2004), 1286 Off. Gaz. Pat. Office 21 (September 7, 2004)). 37 CFR § 41.50(b) provides "[a] new ground of rejection pursuant to this paragraph shall not be considered final for judicial review."

37 C.F.R. § 41.50(b) also provides that the appellant, *WITHIN TWO MONTHS FROM THE DATE OF THE DECISION*, must exercise one of the following two options with respect to the new ground of rejection to avoid termination of the appeal as to the rejected claims:

> (1) *Reopen prosecution.* Submit an appropriate amendment of the claims so rejected or new evidence relating to the claims so rejected, or both, and have the matter reconsidered by the examiner, in which event the proceeding will be remanded to the examiner. . . .
>
> (2) *Request rehearing.* Request that the proceeding be reheard under § 41.52 by the Board upon the same record. . . .

Should the appellant elect to prosecute further before the examiner pursuant to 37 C.F.R. § 41.50(b)(1), in order to preserve the right to seek review under 35 U.S.C. §§ 141 or 145 with respect to the affirmed rejection, the effective date of the affirmance is deferred until conclusion of the prosecution before the examiner unless, as a mere incident to the limited prosecution, the affirmed rejection is overcome.

If the appellant elects prosecution before the examiner and this does not result in allowance of the application, abandonment or a second appeal, this case should be returned to the Board of Patent Appeals and Interferences for final action on the affirmed rejection, including any timely request for rehearing thereof.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED; 37 C.F.R. § 41.50(b)

lbg

LEYDIG, VOIT & MAYER, LTD.
TWO PRUDENTIAL PLAZA, SUITE 4900
180 NORTH STETSON AVENUE
CHICAGO IL 60601-6731